REMARKS

The claims have been amended to place the application in a better condition for allowance. Support for limitation to disorders mediated by the CXCR4 receptor in claim 39 is fully supported by the results shown on pages 32 and 33 of the application which demonstrate clearly that AMD3100 (the therapeutically active compound set forth in the claims) effectively inhibits binding of monoclonal antibodies to the CXCR4 receptor and further inhibits calcium flux induced by SDF-1 binding. (It is to be noted that the results for AMD3100 in Table 3 are in terms of IC_{50} rather than percent inhibition.)

There could be no question that these results are supportive of claim 39. With respect to claim 40, it has been demonstrated that AMD3100 is effective against arthritis in a standard animal model in Example 27 on pages 36-38. With respect to claim 42, page 2, line 21, demonstrates that hematopoiesis is affected by inhibition of CXCR4, and thus leukemias or lymphomas would successfully be treated using this compound. Further, page 2, lines 18-32, show that it was known in the prior art that CXCR4 activity mediates vascularization of the gastrointestinal tract (lines 20-21, claim 46) and cerebellar development (lines 21-22, claim 45). It was also known that cardiogenesis is thus mediated (lines 25, claim 47). The role of CXCR4 in proliferation of glioblastoma tumor cells is also known in the art (page 39, lines 5-7, claim 48).

It is understood, with respect to claims 45-47 that agonist activity may be helpful; however, the ability of AMD3100 to modulate the activity of CXCR4 is nevertheless relevant to these disorders. The interaction of AMD3100 with CXCR4 is clearly desirable in the treatment of arthritis as demonstrated by Example 27 and in the treatment of leukemia, lymphoma, and glioblastoma.

Formal Matters

Applicants note that certain items on the Information Disclosure Statement filed 17 October 2001 are indicated not considered and copies of these documents was requested. These copies are being submitted under separate cover.

A new oath will be submitted; however, as the present application is the national phase of PCT application CA 99/00619 which included an oath from the inventors claiming priority to U.S. 09/111,895, it is believed that the priority has effectively been claimed. In any event, a new oath is submitted in view of the change of inventorship requested hereinbelow.

The title has been amended as requested.

Applicants note the objection to incorporation of essential material by reference to other than a U.S. patent. Applicants are unaware of any location in which an attempt to incorporate essential material has been made; if the Office is aware of such location, its identification is respectfully requested.

Inventorship

Attached hereto is a petition under 37 C.F.R. § 1.48(b) requesting the inventorship herein be amended to name Dominique Schols as sole inventor. The election of subject matter in response to a restriction requirement has resulted in the inventions of the remaining listed co-inventors Bridger, Boehringer, Wang, Skerlj, and Bogucki no longer being claimed. Accordingly, applicants request amendment of the inventorship herein in accordance with the petition.

The Rejections Under 35 U.S.C. § 112, Paragraph 1

The claims were rejected under this paragraph as lacking an enabling written description. It is believed that the amendment to the claims disposes, for the most part, of this rejection. As acknowledged by the Office on page 4 of the Office action - it has been found that compound AMD3100 is a potent and selective CXCR4 antagonist. Applicant is grateful that the Office has

acknowledged that the subject matter of claim 39, as amended, is adequately supported. Thus, it does not matter than AMD3100 does not inhibit M-tropic viruses or that bicyclam (which is in any event not the subject matter of the claims) was found not to inhibit the effects of RANTES, MIP-1α or MCP-3.

The Office then goes on to say that certain chemokine receptors other than CXCR4 are involved in arthritis and transplantation rejection. The thrust of the argument appears to be that therefore CXCR4 is not important. However, the claims are no longer directed to transplantation rejection and arthritis has been shown treatable by AMD3100 in the application itself in an established animal model (Example 27).

Next, the Office objects that no compound has ever been found capable of treating cancer generally in all types. It will be noted that the claims, as amended, are specific to three types of cancer implicated by the knowledge of the funtion of CXCR4 in the prior art - glioblastoma, leukemia and lymphoma.

The Office then cites Gupta, *et al.*, in what appears to be support for the findings made by applicant that AMD3100 which interacts with CXCR4 is effective in treating arthritis. Gupta discloses CXCR4 plays an important role in an inflamatory response. Arthritis is a manifestation of an inflammatory response. The disclosure of Zou, *et al.*, also appears supportive of the credibility of the claims and, indeed, was cited by applicants in support of the claimed subject matter. The Office also cites Tachibana, cited by applicants on page 2 of the specification in support of the subject matter claimed. Again, the fact that other angiogenic regulators also play roles is not in conflict with the fact that CXCR4 plays an important role itself.

In summary, the claims as amended, limited to disorders that are mediated by the activity of the CXCR4 receptor, are clearly supported by the present specification, and, indeed, by much of the art cited by the Office.

The Rejections Under 35 U.S.C. § 112, Paragraph 2

The informalities pointed out in the parentheses/brackets in the named chemical compound - AMD3100 - have been corrected.

Part c of this rejection is believed addressed by amendment. The claims are now limited to disorders mediated by the CXCR4 receptor and these conditions are spelled out in the dependent claims. The Office points out that it is unclear which diseases are associated with each of the chemokine receptors; some of these specific diseases are set forth in the dependent claims. In addition, the target diseases are readily identified experimentally, in any case, by determining whether the CXCR4 receptor activity in a subject is or is not normal. Abnormalities in this activity, which can be established by isolation of cells that display these receptors and testing *ex vivo* can verify the presence of a condition that will be responsive. For example, it is known that certain blood cells contain CXCR4 receptors; these cells can be screened for their ability to respond to CXCR4 agonists and for the ability of known antagonists to inhibit the activity.

The Office points out that clinical parameters remain to be optimized. This is routine; all of the problems identified by the Office are present with respect to every candidate drug. It is well established that these parameters need not be resolved in order to support claims to methods of treatment where a credible basis for these methods has been established. (*In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).) Accordingly, this aspect of the rejection under Paragraph 2 may be withdrawn.

The rejection of claim 44 is mooted by its cancellation.

The Rejections Under 35 U.S.C. § 102

Claims 31 and 39 were rejected under § 102(a) as anticipated by Schols, *et al.*, *J. Exp. Med.* This article is the work of the present applicant; the remaining authors of the article worked under the direction of Dominique Schols.

There is an additional publication also authored by Dr. Schols and individuals working under his direction that appeared in *Antiviral Research* within one year prior to the priority date herein (8 July 1998). The precise publication date of this article has not been established; however, it has been established that it appeared in the August issue and the copy received by the British Library was received 27 August 1997. It is thus unlikely that the actual publication date was prior to 8 July 1997.

Enclosed herewith is a *Katz* declaration by Dr. Schols that the remaining authors of these documents either worked under Dr. Schols' direction or were included on the publication by virtue of their position or because they supplied materials. Accordingly, these documents reflect the invention of Dominique Schols published less than one year prior to the priority date of the present application. In view of the enclosed declaration, these documents may be discounted as prior art since they were not published prior to the invention made by Dominique Schols.

CONCLUSION

The claims have been limited to the use of AMD3100 in treatment of conditions mediated by the chemokine receptor CXCR4. The conditions known to be associated with this receptor are set forth in dependent claims. The inventorship has been corrected under 37 C.F.R. § 1.48(b) to reflect the subject matter claimed. In view of this correction and the enclosed *Katz* declaration, establishing that Dominique Schols is the sole inventor of the claimed subject matter, it is demonstrated that the cited documents are not the basis for rejection over the art. Accordingly, applicants respectfully request that claims 39, 40, 42 and 45-48 be passed to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 391442001122.

Respectfully submitted,

Dated: March 18, 2003 By: Kate H. Murashige

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

39. (Amended) A method for treating or ameliorating at least one [chemokine mediated] disorder[,] mediated by the CXCR4 receptor which method comprises administering to a subject in need of such treatment or amelioration an effective amount of [the] a pharmaceutical composition [of claim 31] comprising a therapeutically effective amount of 1,1'-[1,4-(phenylenebis(methylene))]bis-1,4,8,11-tetraazacyclotetradecane.

42. (Amended) The method of claim 39 wherein said disorder is [cancer] leukemia or lymphoma.

46. (Amended) The method of claim 39 wherein said disorder is vasculature development disease of the gastrointestinal tract.